Claims

We claim:

1. A targeting construct comprising:

(a) a first polynucleotide sequence homologous to a target gene, wherein the target gene is selected from the group consisting of a retina-specific nuclear receptor gene

(c) a second polynucleotide sequence homologous to the target gene; and

(d) a selectable marker.

2. The targeting construct of claim 1, wherein the targeting construct further comprises a screening marker.

3. A method of producing a targeting construct for a retina-specific nuclear receptor gene, the method comprising:

(a) obtaining a first polynucleotide sequence homologous to a target gene;

(b) obtaining a second polynucleotide sequence homologous to the target gene;

(c) providing a vector comprising a selectable marker; and

(d) inserting the first and second sequences into the vector, to produce the targeting construct.

4. A method of producing a targeting construct for a retina-specific nuclear receptor gene, the method comprising:

(a) providing a polynucleotide sequence homologous to the target gene;

(b) generating two different fragments of the polynucleotide sequence;

(c) providing a vector having a gene encoding a selectable marker; and

(d) inserting the two different fragments into the vector to form the targeting construct.

5. A cell comprising a disruption in a a retina-specific nuclear receptor gene.

6. The cell of claim 5, wherein the cell is a murine cell.

7. The cell of claim 6, wherein the murine cell is an embryonic stem cell.

8. A non-human transgenic animal comprising a disruption in a retina-specific nuclear receptor gene.

9. A cell derived from the non-human transgenic animal of claim 8.

10. A method of producing a transgenic mouse comprising a disruption in a retina-specific nuclear receptor gene, the method comprising:

(a) introducing the targeting construct of claim 1 into a cell;

(b) introducing the cell into a blastocyst;

(c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and

(d) breeding the chimeric mouse to produce the transgenic mouse.

11. A method of identifying an agent that modulates the expression of a retina-specific nuclear receptor gene, the method comprising:

(a) providing a non-human transgenic animal comprising a disruption in a retina-specific nuclear receptor gene;

(b) administering an agent to the non-human transgenic animal; and

(c) determining whether the expression of the disrupted gene in the non-human transgenic animal is modulated.

12. A method of identifying an agent that modulates the function of a retina-specific nuclear receptor gene, the method comprising:

(a) providing a non-human transgenic animal comprising a disruption in a retina-specific nuclear receptor gene gene;

(b) administering an agent to the non-human transgenic animal; and

(c) determining whether the function of the disrupted a retina-specific nuclear receptor gene in the non-human transgenic animal is modulated.

13. A method of identifying an agent that modulates the expression of a retina-specific nuclear receptor gene, , the method comprising:

(a) providing a cell comprising a disruption in a retina-specific nuclear receptor gene gene;

(b) contacting the cell with an agent; and

(c) determining whether expression of the retina-specific nuclear receptor gene is modulated.

14. A method of identifying an agent that modulates the function of a retina-specific nuclear receptor gene, the method comprising:

(a) providing a cell comprising a disruption in a retina-specific nuclear receptor gene gene;

(b) contacting the cell with an agent; and

(c) determining whether the function of the retina-specific nuclear receptor gene is modulated.

15. The method of claim 13 or claim 14, wherein the cell is derived from the non-human transgenic animal of claim 8.

16. An agent identified by the method of claim 11, claim 12, claim 13, or claim 14.

17. A transgenic mouse comprising a disruption in a retina-specific nuclear receptor gene, wherein the transgenic mouse exhibits an eye abnormality.

18. The transgenic mouse of claim 17, wherein the eye abnormality is a retinal abnormality.

19. The transgenic mouse of claim 18, wherein the retinal abnormality is characterized by retinal dysplasia.

20. The transgenic mouse of claim 19, wherein the transgenic mouse exhibits at least one of the following characteristics: rosette formation in the retina, retinal folding, segmental thinning or absence of the outer nuclear layer of the retina, or absence of the retina.

21. The transgenic mouse of claim 17, wherein the transgenic mouse is heterozygous for a disruption in a retina-specific nuclear receptor gene.

22. The transgenic mouse of claim 17, wherein the transgenic mouse is homozygous for a disruption in a retina-specific nuclear receptor gene.

23. A method of producing a transgenic mouse comprising a disruption in a retina-specific nuclear receptor gene, wherein the transgenic mouse exhibits an eye abnormality, the method comprising:

(a) introducing a retina-specific nuclear receptor gene targeting construct into a cell;

(b) introducing the cell into a blastocyst;

(c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and

(d) breeding the chimeric mouse to produce the transgenic mouse comprising a disruption in a retina-specific nuclear receptor gene.

24. A cell derived from the transgenic mouse of claim 17 or claim 23, wherein the cell comprises a disruption in a retina-specific nuclear receptor gene.

25. A method of identifying an agent that ameliorates an eye abnormality, the method comprising:

(a) administering an agent to a transgenic mouse comprising a disruption in a retina-specific nuclear receptor gene; and

(b) determining whether the agent ameliorates the eye abnormality of the transgenic mouse.

26. The method of claim 25, wherein the eye abnormality is a retinal abnormality.

27. The method of claim 26, wherein the retinal abnormality is characterized by retinal dysplasia.

28. The method of claim 27, wherein the transgenic mouse exhibits at least one of the following characteristics: rosette formation in the retina, retinal folding, segmental thinning or absence of the outer nuclear layer of the retina, or absence of the retina.

29. A method of identifying an agent which modulates retina-specific nuclear receptor gene expression, the method comprising:

(a) administering an agent to the transgenic mouse comprising a disruption in a retina-specific nuclear receptor gene; and

(b) determining whether the agent modulates retina-specific nuclear receptor gene expression in the transgenic mouse, wherein the agent modulates a phenotype associated with a disruption in a retina-specific nuclear receptor gene.

30. The method of claim 30, wherein the phenotype comprises any one of the following: an eye abnormality.

31. A method of identifying an agent which modulates a phenotype associated with a disruption in a retina-specific nuclear receptor gene, the method comprising:

(a) administering an agent to a transgenic mouse comprising a disruption in a retina-specific nuclear receptor gene; and

(b) determining whether the agent modulates the phenotype.

32. The method of claim 31, wherein the phenotype comprises an eye abnormality.

33. A method of identifying an agent which modulates retina-specific nuclear receptor gene expression, the method comprising:

(a) providing a cell comprising a disruption in a retina-specific nuclear receptor gene;

(b) contacting the cell with an agent; and

(c) determining whether the agent modulates retina-specific nuclear receptor gene expression, wherein the agent modulates a phenotype associated with a disruption in a retina-specific nuclear receptor gene.

34. The method of claim 34, wherein the phenotype comprises an eye abnormality.

35. A method of identifying an agent which modulates retina-specific nuclear receptor gene function, the method comprising:

(a) providing a cell comprising a disruption in a retina-specific nuclear receptor gene;

(b) contacting the cell with an agent; and

(c) determining whether the agent modulates retina-specific nuclear receptor gene function, wherein the agent modulates a phenotype associated with a disruption in a retina-specific nuclear receptor gene.

36. The method of claim 35, wherein the phenotype comprises an eye abnormality.

37. An agent identified by the method of claim 25, claim 29, claim 31, claim 33 or claim 35.

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